Remarks and Arguments

Claims 1-23 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the examiner has stated that the claims are improper because they are method claims that do not correctly list a series of method steps. Thus, Claim 1, from which each of the other claims ultimately depends, has been amended to recast the claim as a series of method steps without narrowing its scope. Claim 7 was also rejected for lacking antecedent basis for the term "the internucleotide cyanoethyl phosphate bond." Claim 7 has therefore been amended to read "an internucleotide cyanoethyl phosphate bond." Reconsideration of Claims 1-23 under these grounds for rejection is respectfully requested.

Claims 22 and 23 were objected to for use of the word "streptavidine." These claism have therefore been amended to make use instead of the spelling "streptavidin." Reconsideration of Claims 22 and 23 under this ground for rejection is respectfully requested.

Claims 1-6 were provisionally rejected for obviousness-type double patenting in view of U.S. Patent Application No. 10/079,271. As this rejection is currently a provisional rejection, applicants have chosen not to respond substantively at this time, particularly considering the amendments to the claims in question. Should this rejection be maintained in the future, it will be addressed on a substantive level. Reconsideration of Claims 1-6 under this ground for rejection if respectfully requested.

Claims 1-6, 18 and 21-23 are rejected under 35 U.S.C. §102(b) as being anticipated by PCT Application Publication No. WO 97/27325 ("Van Ness"). In making this rejection, the examiner has stated that Van Ness "teaches a method for mass spectrometric analysis of known mutation sites in genome DNA by mutation-dependent primer extension, wherein the nucleotide chain of the extension primer contains a photocleavable linker which is cleaved by UV light irradiation before mass spectrometric analysis." This is a direct quote from applicants' original Claim 1, which the examiner

compares to various sections of the Van Ness reference. However, closer examination reveals that significant differences exist between Van Ness and the present invention.

Van Ness discloses a method for genotyping a selected organism having tagged nucleic acid molecules from a selected target molecule. Each tag is correlated with a particular fragment, and may be detected by non-fluorescent spectrometry or potentiometry. In fact, the "particular fragment" is a compound of the class of photocleavable o-nitrobenzyl derivatives. Van Ness uses this particular fragment for the connection of the terminal tag and the selected target molecule, which could be synthesized by automated DNA synthesis as 5'-aminohexyl tailed oligonucleotide. This means that the incorporation of the tag molecule equipped with a photocleavable moiety has to be done after DNA synthesis, and requires an additional synthesis step. Moreover, Van Ness teaches the detection of the tag molecule after photolytical cleavage from the remainder of the compound.

In contrast with Van Ness, the present invention teaches a method for performing a mass spectrometric analysis of known mutation sites in genomic DNA. In particular, an extension primer is used that has a photocleavable linker, and is attached to the DNA adjacent to the mutation site. The primer is then extended using a mutation dependent primer extension to form a DNA segment containing information regarding the mutation site. The photocleavable linker is then cleaved to produce a DNA cleavage product containing the relevant information, and is analyzed by mass spectrometry.

The present invention has in common with Van Ness the use of a photolytic cleavage function. However, the overall processes of the two methods are completely different. Whereas Van Ness is attaching a tag molecule to a selected molecule and using the tag to identify a particular fragment, the present invention uses a primer designed to isolate a mutation, and includes with it a photocleavable linker that allows a short segment that contains information regarding the mutation to be cleaved for the purposes of mass spectrometry. Thus, where the present invention is specifically

directed to the generation of short strands having information regarding a mutation site, Van Ness seems to be unconcerned with such a procedure. Claim 1, as amended, clearly recites the steps of providing an extension primer having a photocleavable linker, and attaching it adjacent to a mutation site, extending the primer using mutation dependent primer extension, cleaving the linker to produce a DNA cleavage product and analyzing the cleavage product by mass spectrometry. Nowhere in Van Ness is there any suggestion whatsoever of such a method. Thus, despite the use by Van Ness of a photolytical cleavage for other purposes, Claim 1 is completely unsuggested by the Van Ness reference. Claims 2-6, 18 and 21-23 each depend ultimately from Claim 1, and are therefore equally unsuggested by the cited prior art. Reconsideration of Claims 1-6, 18 and 21-23 under this ground for rejection is respectfully requested.

Claims 7-17 and 19-20 were rejected under 35 U.S.C. §103(a) as being obvious over Van Ness in view of PCT Application Publication No. WO 96/272,681 ("Gut"), and in further view of the Nucleic Acids Research article by Sauer et al. ("Sauer"). In making this rejection, the examiner cites Van Ness for the same reasons as used in the rejection of Claim 1. The Sauer reference is added as showing the use of various materials recited in applicants' dependent claims. The office action is silent as to the reason for citing the Gut reference. Indeed, the Gut reference is not listed on any form PTO 1449 or PTO 892 currently in the application file. Thus, it is possible that the mention of this reference in the body of the office action was a clerical error. Nevertheless, the Gut reference is discussed briefly below.

Gut discloses a method of DNA analysis by mass spectrometry involving an introduction of modified primers and substrates that makes the nucleotides more susceptible to measurement as modified copy reaction product using mass spectrometry. Gut discloses modification steps that include the elimination of the negative charges of the DNA sugar-phosphate backbone by use of alkylated phosphorothioates and the introduction of a charge tag to controllably ionize the product DNA molecule. Gut first introduces the phosphorothioates and charge tags using modified primers or dNTPs in a linear enzymatic copy reaction using DNA polymerase,

and then performs methylation of this copy reaction product in a chemical step. The use of charge tags allows for much higher sensitivity in the mass spectrometric analysis of the modified DNA.

Sauer discloses a method for genotyping single nucleotide polymorphisms (SNPs) by performing a polymerase chain reaction that surrounds a region containing a known SNP. dNTPs are enzymatically destroyed with shrimp alkaline phosphatase, and a charge-tag containing extension primer, a conditioned set of α-dNTPs and α-ddNTPs and DNA polymerase are used for the generation of allele specific products in a primer extension reaction. The unmodified DNA is removed by 5'-phosphodiesterase digestion and the modified products are alkylated to increase the detection sensitivity in the mass spectrometric analysis using the non-protonating α-cyano-4-hydroxycinnamic acid methyl ester matrix.

Despite Sauer's being directed to the genotyping of SNPs, neither Gut nor Sauer, either alone or in combination with each other and Van Ness, appear to suggest the use of a photocleavable linker for the generation of shortened DNA fragments containing information about a mutation site. Therefore, in the overall prior art combination, there appears to be no suggestion of a method as laid out in applicants' Claim 1, that is, a method for providing an extension primer having a photocleavable linker, and attaching it adjacent to a mutation site, extending the primer using mutation dependent primer extension, cleaving the linker to produce a DNA cleavage product and analyzing the cleavage product by mass spectrometry. Each of Clamis 7-17 and 19-20 depend ultimately from Claim 1 and are therefore likewise unsuggested by the cited prior art. Reconsideration of Claims 7-17 and 19 20 under this ground for rejection is respectfully requested.

Several additional non-substantive amendments have been made to certain claims to correct grammatical errors or to provide better agreement with the language of claims from which they depend.

In light of the foregoing amendments and remarks, it is respectfully requested that all the claims be allowed such that the application may be passed to issue. If it is believed that a telephone conference will help expedite prosecution of the application,

the examiner is invited to call the undersigned. The Commissioner is hereby authorized to charge any fees due for the filing of this paper to applicants' attorneys' Deposit Account No. 02-3038.

Respectfully submitted

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